4/4

IN THE UNITED STATES PATENT OFFICE

In re: Klimko et al.

Serial No. NYA

Filed: August 21, 1997

For: USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

CERTIFICATE OF MAILING BY EXPRESS MAIL

I hereby certify that this correspondence is being deposited with the United States Postal Service as "Express Mail," Mailing Label No. EM367125014US in an envelope addressed to: Assistant Commissioner for Patents, Box Patent Applications, Washington, D.C. 20231 on this date:

8-21-97
Date

Dawn Fedyniak
Dawn Fedyniak

Assistant Commissioner for Patents
Box: Patent Applications
Washington, D.C. 20231

Sir:

This is a request for filing a (_X_ Continuation / ___ Divisional) application under Rule 60 of pending:

Serial No. 08/769,293, filed December 18, 1996

1. _X_ Enclosed is a copy of the prior application as originally filed (including the specification (with claims) drawings, and oath or declaration); and I hereby verify that such copy is a true copy of the prior complete application.

2. _X_ Enclosed is a Preliminary Amendment.

3. _X_ Enclosed is a copy of the Petition for Correction of Inventorship (with supporting statements and consents) filed pursuant to 37 CFR § 1.48 in the prior application to include Paul W. Zinke as a co-inventor.

4. Enclosed is Form PTO-1449, along with Information Disclosure Statement, listing and enclosing copies of thirty-three (33) references.

5. X The filing fee is calculated below:

CLAIMS AS AMENDED BY PRELIMINARY AMENDMENT

FOR	NO. FILED	NO. EXTRA	RATE	TOTALS
TOTAL CLAIMS	22 __- 20	2	$ 22.00	44.00
INDEPENDENT CLAIMS	2 ___ 3	0	$ 80.00	0.00
XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXX			*BASIC FEE*	$770.00
			TOTAL FEE	$814.00

6. X Please charge the $814.00 filing fee to Deposit Account No. 01-0682. A duplicate copy of this sheet is enclosed

7. X The Commissioner is hereby authorized to charge any additional fees which may be required or credit any overpayment to Deposit Account No. 01-0682. A duplicate copy of this sheet is enclosed.

8. X Cancel in this application original claims [see Preliminary Amendment of the prior application before calculating filing fee].

9. __ Amend the specification by inserting before the first line the sentence:

10. __ Transfer the drawings from the prior application to this application and abandon said prior application as of the filing date accorded this application. A duplicate copy of this sheet is enclosed for filing in the prior application file.

11. X The prior application is assigned to Alcon Laboratories, Inc.

12. X The power of attorney in the prior application is to James A. Arno, Reg. No. 26,145; Gregg C. Brown, Reg. No. 30,613; Sally Yeager, Reg. No. 32,757; Julie J. L. Cheng, Reg. No. 33,848; Barry L. Copeland, Reg. No. 34,801; Jeffrey S. Schira, Reg. No. 34,922 and Patrick M. Ryan, Reg. No. 36,263 of Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, Texas 76134; and Robert L. Price of Lowe, Price, LeBlanc & Becker, Suite 300, 99 Canal Center Plaza, Alexandria, Virginia 22314.

a. X The power appears in the original papers of the prior application.

b. __ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

c. X Please address all future communications to:

Barry L. Copeland
Patent Department (Q-148)
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
(817) 551-4322

Respectfully submitted,

ALCON LABORATORIES, INC.

8-21-97
Date

Barry L. Copeland
Registration No. 34,801

Barry L. Copeland
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Docket No. 1407B

IN THE UNITED STATES PATENT OFFICE

In re: Klimko et al.

Serial No. NYA

Filed: August 21, 1997

For: USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

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8-21-97
Date

Dawn Fedyniak
Dawn Fedyniak

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
BOX Patent Applications
Washington, DC 20231

Dear Sir:

Please consider the following amendments and remarks prior to the examination of this application.

Please amend the application to include Paul W. Zinke as an inventor. A copy of the Petition for Correction of Inventorship and supporting statements as filed in the parent application to this application are submitted herewith.

IN THE SPECIFICATION

At page 1, in the first line of text after the title of the invention, after "The present application" insert:

--is a continuation of U.S. Patent Application Serial No. 08/769,293, filed December 18, 1996, now U.S. Patent No. 5,665,773, which is a continuation of U.S. Patent Application Serial No. 08/280,681, filed July 26, 1994, now abandoned, which--.

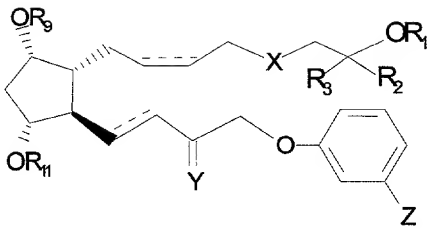
At page 1, in the second line of text after the title of the invention, after "August 3, 1993" insert --, now U.S. Patent No. 5,510,383--.

IN THE CLAIMS

Please cancel all pending claims, and add the following new claims:

--24. A method of treating glaucoma and ocular hypertension which comprises topically administering to the affected eye a composition comprising a therapeutically effective amount of a compound having the absolute stereochemical structure of the following formula (IV), and being substantially free of the enantiomer

of said compound:



(IV)

wherein:

R_1 = H; C_1-C_{12} straight-chain or branched alkyl; C_1-C_{12} straight-chain or branched acyl; C_3-C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 = H, or C_1-C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X = O, S, or CH_2;

---- represents any combination of a single bond, or a *cis* or *trans* double bond for the alpha (upper) chain; and a single bond or *trans* double bond for the omega (lower) chain;

R_9 = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

R_{11} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

Y = O; or H and OR_{15} in either configuration wherein R_{15} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl; and

Z = Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$-C_{12} straight-chain or branched acyl; and when $R_2 = R_3$ = H, then $R_1 \neq$ a cationic salt moiety; and

with the further proviso that the following compound be excluded:

cyclopentane heptenol-5-*cis*-2-(3-αhydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5 dihydroxy, [1_α, 2_β, 3_α, 5_α].

25. The method of claim 24, wherein for the compound (IV):

R_2, R_3 taken together represent O;

X = CH_2;

--- represents a *cis* double bond for the alpha (upper) chain and a *trans* double bond for the omega (lower) chain;

R_9 and R_{11} = H; and

Y = OH in the alpha configuration and H in the beta configuration.

26. The method of claim 25, wherein for the compound (IV): Z = CF_3.

27. The method of claim 24, wherein: $R_2 = R_3$ = H, or R_2 and R_3 taken together represent O; X = O or CH_2; $R_9 = R_{11}$ = H; Y = H and OR_{15}; and R_{15} = H.

28. The method of claim 27, wherein: R_1 = H, C_1-C_{12} straight chain or branched alkyl or cationic salt moiety; and R_2 and R_3 taken together represent O.

29. The method of claim 28, wherein the compound of formula (IV) is selected from the group consisting of 3-oxacloprostenol, 13,14-dihydrofluprostenol, and their pharmaceutically acceptable esters and salts.

30. The method of claim 27, wherein: R_1 = H or C_1-C_{12} straight chain or branched acyl; and $R_2 = R_3$ = H.

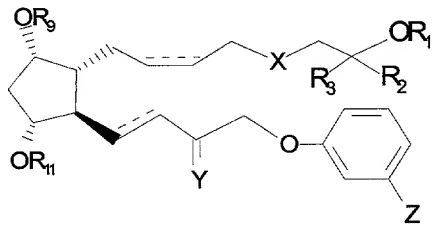
31. The method of claim 30, wherein the compound formula (IV) is 13,14-dihydrocloprostenol pivaloate.

32. The method of claim 24, wherein between about 0.01 and about 1000 μg/eye of the compound is administered.

33. The method of claim 32, wherein between about 0.1 and about 100 μg/eye of the compound is administered.

34. The method of claim 33, wherein between about 0.1 and about 10 μg/eye of the compound is administered.

35. A topical ophthalmic composition for the treatment of glaucoma and ocular hypertension comprising an ophthalmically acceptable carrier and a therapeutically effective amount of a compound having the absolute stereochemical structure of the following formula (IV), and being substantially free of the enantiomer of said compound:



(IV)

wherein:

R_1 = H; C_1-C_{12} straight-chain or branched alkyl; C_1-C_{12} straight-chain or branched acyl; C_3-C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 = H, or C_1-C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X = O, S, or CH_2;

---- represents any combination of a single bond, or a *cis* or *trans* double bond for the alpha (upper) chain; and a single bond or *trans* double bond for the omega (lower) chain;

R_9 = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

R_{11} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

Y = O; or H and OR_{15} in either configuration wherein R_{15} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl; and

Z = Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$-C_{12} straight-chain or branched acyl; and when $R_2 = R_3$ = H, then $R_1 \neq$ a cationic salt moiety; and

with the further proviso that the following compound be excluded:

cyclopentane heptenol-5-*cis*-2-(3-αhydroxy-4-m-chlorophenoxy-1-trans-butenyl)-3,5 dihydroxy, [1_α, 2_β, 3_α, 5_α].

36. The composition of claim 35, wherein for the compound (IV):

R_2, R_3 taken together represent O;

X = CH_2;

--- represents a *cis* double bond for the alpha (upper) chain and a *trans* double bond for the omega (lower) chain;

R_9 and R_{11} = H; and

Y = OH in the alpha configuration and H in the beta configuration.

37. The composition of claim 36, wherein for the compound (IV): Z = CF_3.

38. The composition of claim 35, wherein: $R_2 = R_3$ = H, or R_2 and R_3 taken together represent O; X = O or CH_2; $R_9 = R_{11}$ = H; Y = H and OR_{15}; and R_{15} = H.

39. The composition of claim 38, wherein: R_1 = H, C_1-C_{12} straight chain or branched alkyl, or cationic salt moiety; and R_2 and R_3 taken together represent O.

40. The composition of claim 39, wherein the compound of formula (IV) is selected from the group consisting of 3-oxacloprostenol, 13,14-dihydrofluprostenol, and their pharmaceutically acceptable esters and salts.

41. The composition of claim 38, wherein: R_1 = H or C_1-C_{12} straight chain or branched acyl; and R_2 = R_3 = H.

42. The composition of claim 41, wherein the compound of formula (IV) is dihydrocloprostenol pivaloate.

43. The composition of claim 35, wherein the concentration of the compound of formula (IV) is between about 0.0003 and about 0.3 wt%.

44. The composition of claim 43, wherein the concentration of the compound of formula (IV) is between about 0.0003 and about 0.3 wt%.

45. The composition of claim 44, wherein the concentration of the compound of formula (IV) is between about 0.003 and about 0.03 wt%.--.

REMARKS

This application is a Rule 60 continuation of U.S. Patent Application Serial No. 08/769,293, expected to issue shortly as U.S. Patent No. 5,665,773 (the "Parent Application"), which is a file wrapper continuation of U.S. Patent Application Serial No. 08/280,681, now abandoned, which was a continuation-in-part of U.S. Patent

Application Serial No. 08/101,598, now U.S. Patent No. 5,510,383. In addition to updating this patent history, the present Amendment cancels the pending claims for the present application and replaces them with new claims 24-45. As will be explained in more detail below, the new claims generally correspond to the allowed claims of the Parent Application, but are directed to compositions comprising specific isomers of the compounds, and being substantially free of the enantiomers thereof.

Claim 24, added by the present amendment, corresponds to allowed claim 1 of the Parent Application. The Examiner will note that there are two differences between newly added claim 24 and claim 1 of the Parent Application. First, whereas the independent claim of the Parent Application is directed to a method comprising the topical administration of a compound of formula IV, the method of claim 24 comprises administering a "composition comprising a therapeutically effective amount of a compound <u>having the absolute stereochemical structure of the following formula (IV), and being substantially free of the enantiomer of said compound...</u>" (emphasis added). Those skilled in the art will appreciate that the compounds of formula (IV) are all chiral compounds. Each such compound will have two enantiomers, that have the same relative configuration, but are mirror images of each other. All of the presently added claims are directed to compounds having the absolute stereochemical structure defined by formula (IV) in a composition that is substantially free of the mirror-image compound, i.e. the enantiomer. Support for this amendment is found in the specification in Table I and Examples 1-4 at pages 7-23. Each of the synthetic examples (1-4), describe chiral syntheses of the desired compounds. That is to say that the yield of each such synthesis would be an enantiomerically pure compound which, by definition, would be substantially free of its enantiomer. Because the syntheses described in Examples 1-4 are "representative in nature" (page 6, line 7), they support the "absolute stereochemical" limitation for all of the compounds of formula (IV). Consequently, the applicants respectfully submit that the claim limitations added by the present

amendment are fully support by the specification and do not constitute the addition of new matter.

The second difference the Examiner will note between the presently amended claim 24 and claim 1 of the allowed parent application lies in the "proviso" excluding certain compounds from the scope of the claim. Excluded from the scope of the independent claim in the parent application were cloprostenol, fluprostenol and their analogs, which had been claimed in an earlier application (U.S. Application Serial No. 08/101,598, now U.S. Patent No. 5,510,383). Because none of the claims of that prior application contain limitations requiring that the compound be enantiomerically pure, it is not necessary to exclude those compounds from the presently amended claims. Support for the amendment is found at pages 3 and 4 of the specification where the description of the compounds of formula (IV) does not exclude cloprostenol, fluprostenol and their analogs. Applicants respectfully submit, therefore, that this component of the present amendment is also supported by the specification, adds no new matter, and creates no obviousness-type double patenting problem relative to any of the prior applications.

Newly added claims 25 and 26 depend from claim 24 and are limited to cloprostenol, fluprostenol and their analogs. Cloprostenol and fluprostenol are disclosed in the specification at pages 1 and 2, as structures II and III, respectively.

Added claims 27-34 track allowed claims 2-9 of the Parent Application.

Added claims 35-45 are ophthalmic composition claims that correspond generally to the allowed composition claims of the Parent Application. Thus, independent claim 35 corresponds to allowed claim 10 of the Parent Application with the two differences discussed above relative to added claim 24. Claims 36 and 37 correspond to the added method claims 25 and 26 covering cloprostenol,

fluprostenol and their analogs. Claims 38-45 track allowed claims 11-18 of the Parent Application. There are no claims added by the present amendment which correspond to allowed claims 19 and 20 of the Parent Application. For the reasons set forth above concerning the added method claims, the applicants respectfully submit that the ophthalmic composition claims added by the present amendment are supported by the specification, add no new matter, and create no obviousness-type double patenting problem relative to prior applications.

The applicants consider the amended claims to be in condition for allowance, and respectfully request the Examiner's favorable consideration.

Respectfully submitted,

ALCON LABORATORIES, INC.

Date: 8-21-99 By: _____

Barry L. Copeland
Reg. No. 34,801

Barry L. Copeland
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Attorney Docket No. 1407B

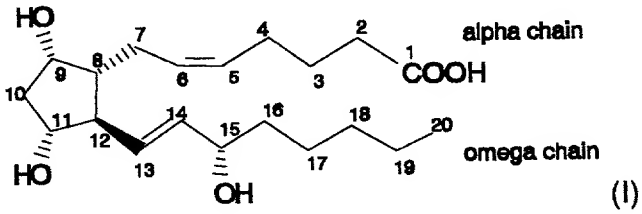
USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

The present application is a continuation-in-part of U.S. Patent Application Serial Number 08/101,598 filed August 3, 1993.

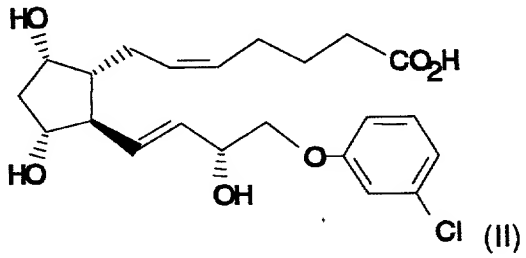
BACKGROUND OF THE INVENTION

The present invention relates to the treatment of glaucoma and ocular hypertension. In particular, the present invention relates to the use of cloprostenol and fluprostenol analogues for the treatment of glaucoma and ocular hypertension.

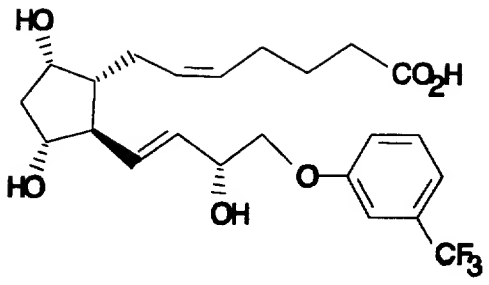
Cloprostenol and fluprostenol, both known compounds, are synthetic analogues of $PGF_{2\alpha}$, a naturally-occurring F-series prostaglandin (PG). Structures for $PGF_{2\alpha}$ (I), cloprostenol (II), and fluprostenol (III), are shown below:



(I)



(II)



(III)

The chemical name for cloprostenol is 16-(3-chlorophenoxy)-17,18,19,20-tetranor $PGF_{2\alpha}$. Monograph No. 2397 (page 375) of The Merck Index, 11th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of cloprostenol. Fluprostenol has the chemical name 16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor $PGF_{2\alpha}$. Monograph No. 4121 (pages 656-657) of The Merck Index, 11th Edition (1989) is incorporated herein by reference to the extent that it describes the preparation and known pharmacological profiles of fluprostenol. Cloprostenol and fluprostenol are 16-aryloxy PGs and, in addition to the substituted aromatic ring, differ from the natural product $PGF_{2\alpha}$ in that an oxygen atom is embedded within the lower (omega) chain. This oxygen interruption forms an ether functionality.

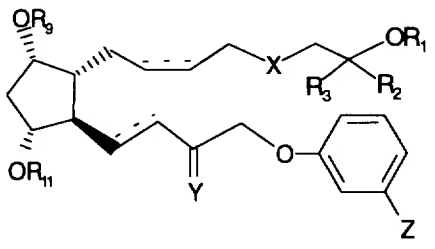
Naturally-occurring prostaglandins are known to lower intraocular pressure (IOP) after topical ocular instillation, but generally cause inflammation, as well as surface irritation characterized by conjunctival hyperemia and edema. Many synthetic prostaglandins have been observed to lower intraocular pressure, but such compounds also produce the aforementioned side effects which severely restrict clinical utility.

SUMMARY OF THE INVENTION

It has now been unexpectedly found that certain novel cloprostenol and fluprostenol analogues are useful in treating glaucoma and ocular hypertension. In particular, topical application of ophthalmic compositions comprising these novel cloprostenol and fluprostenol analogues result in significant IOP reduction.

DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the present invention have the following general formula:



(IV)

wherein:

R_1 = H; C_1-C_{12} straight-chain or branched alkyl; C_1-C_{12} straight-chain or branched acyl; C_3-C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 = H, or C_1-C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X = O, S, or CH_2;

---- represents any combination of a single bond, or a *cis* or *trans* double bond for the alpha (upper) chain; and a single bond or *trans* double bond for the omega (lower) chain;

R_9 = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

R_{11} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

Y = O; or H and OR_{15} in either configuration wherein R_{15} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl; and

Z = Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$-C_{12} straight-chain or branched acyl; and when $R_2 = R_3$ = H, then $R_1 \neq$ a cationic salt moiety.

As used herein, the term "cationic salt moiety" includes alkali and alkaline earth metal salts as well as ammonium salts.

Preferred compounds include the 3-oxa form of cloprostenol isopropyl ester (Table, 1, compound **5**), 13,14-dihydrofluprostenol isopropyl ester (compound **6**), cloprostenol-1-ol (compound **7**), and 13,14-dihydrocloprostenol-1-ol pivaloate (compound **8**).

The compounds of formula (IV) are useful in lowering intraocular pressure and thus are useful in the treatment of glaucoma. The preferred route of administration is topical. The dosage range for topical administration is generally between about 0.01 and about 1000 micrograms per eye (µg/eye), preferably between about 0.1 and about 100 µg/eye, and most preferably between about 1 and 10 µg/eye. The compounds of the present invention can be administered as solutions, suspensions, or emulsions (dispersions) in a suitable ophthalmic vehicle.

In forming compositions for topical administration, the compounds of the present invention are generally formulated as between about 0.00003 to about 3 percent by weight (wt%) solutions in water at a pH between 4.5 to 8.0. The compounds are preferably formulated as between about 0.0003 to about 0.3 wt% and, most preferably, between about 0.003 and about 0.03 wt%. While the precise

regimen is left to the discretion of the clinician, it is recommended that the resulting solution be topically applied by placing one drop in each eye one or two times a day.

Other ingredients which may be desirable to use in the ophthalmic preparations of the present invention include preservatives, co-solvents and viscosity building agents.

Antimicrobial Preservatives:

Ophthalmic products are typically packaged in multidose form, which generally require the addition of preservatives to prevent microbial contamination during use. Suitable preservatives include: benzalkonium chloride, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, ONAMER M®, or other agents known to those skilled in the art. Such preservatives are typically employed at a concentration between about 0.001% and about 1.0% by weight.

Co-Solvents:

Prostaglandins, and particularly ester derivatives, typically have limited solubility in water and therefore may require a surfactant or other appropriate co-solvent in the composition. Such co-solvents include: Polysorbate 20, 60 and 80; Pluronic F-68, F-84 and P-103; Tyloxapol ®; Cremophor® EL; sodium dodecyl sulfate; glycerol; PEG 400; propylene glycol; cyclodextrins; or other agents known to those skilled in the art. Such co-solvents are typically employed at a concentration between about 0.01% and about 2% by weight.

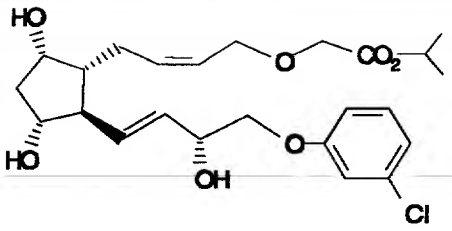
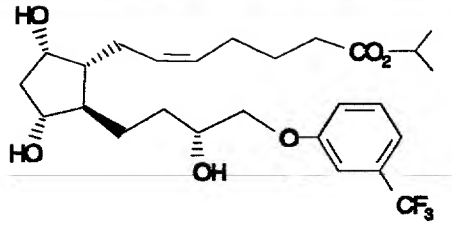
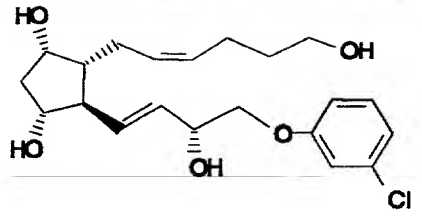
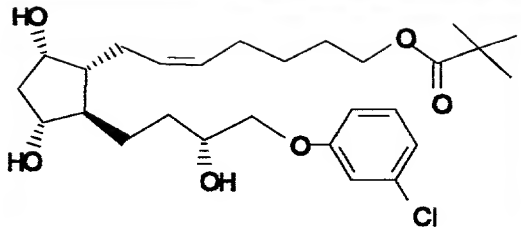
Viscosity Agents:

Viscosity greater than that of simple aqueous solutions may be desirable to increase ocular absorption of the active compound, to decrease variability in dispensing the formulations, to decrease physical separation of components of a suspension or emulsion of formulation and/or otherwise to improve the ophthalmic

formulation. Such viscosity building agents include, for example, polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxy propyl methylcellulose, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxy propyl cellulose or other agents known to those skilled in the art. Such agents are typically employed at a concentration between about 0.01% and about 2% by weight.

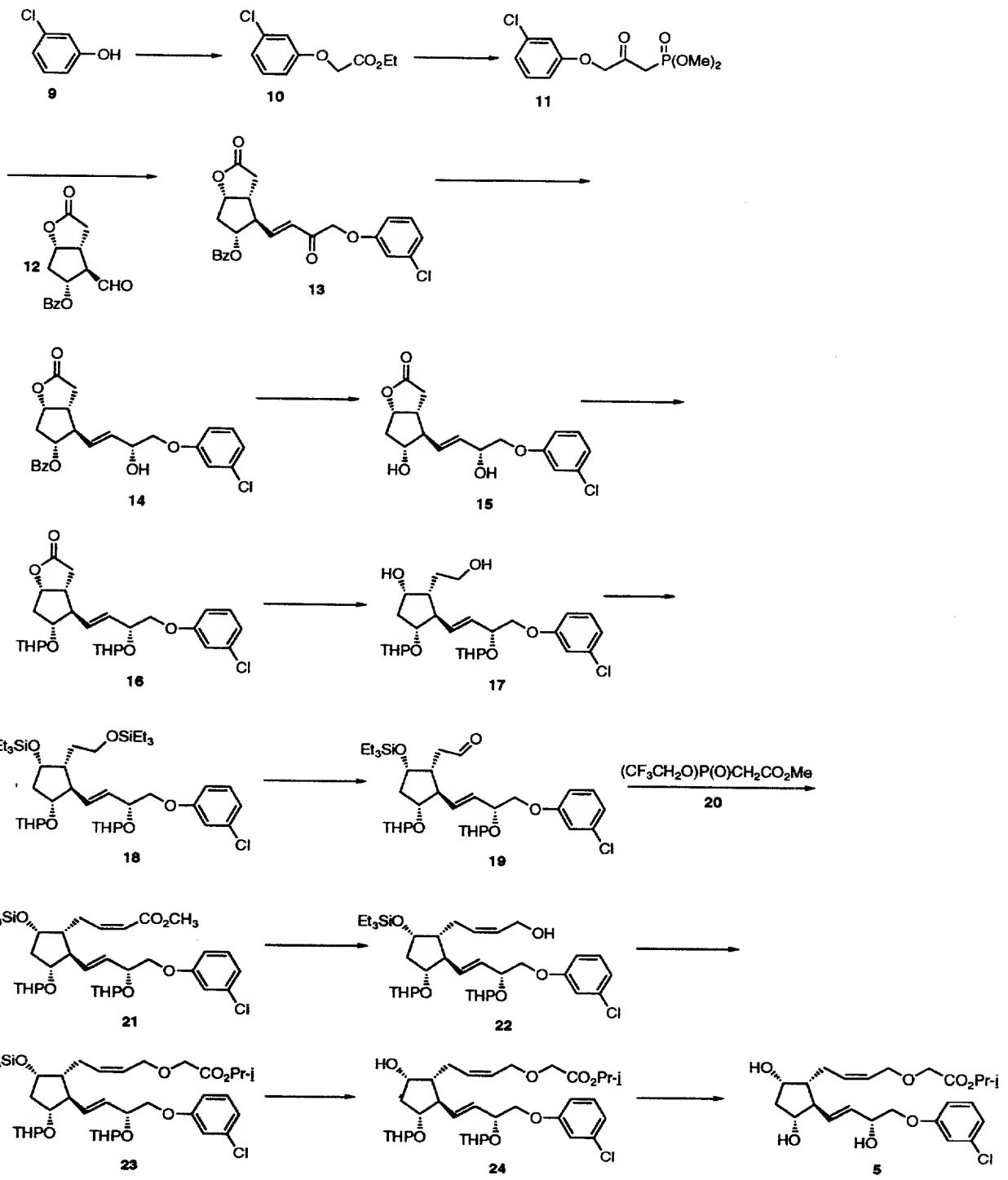
The following Examples 1-4 describe the synthesis of compounds **5-8** (Table 1). These syntheses are representative in nature and are not intended to be limiting. Other compounds of formula (IV) may be prepared using analogous techniques known to those skilled in the art.

Table 1

	COMPOUND NAME	COMPOUND STRUCTURE
5	3-oxacloprostenol isopropyl ester	
6	13,14-dihydrofluprostenol isopropyl ester	
7	cloprostenol-1-ol	
8	13,14-dihydrocloprostenol-1-ol pivaloate	

In the examples below, the following standard abbreviations are used: g = grams (mg = milligrams); mol = moles (mmol = millimoles); mol% = mole percent; mL = milliliters; mm Hg = millimeters of mercury; mp = melting point; bp = boiling point; h = hours; and min = minutes. In addition, "NMR" refers to nuclear magnetic resonance spectroscopy and "Cl MS" refers to chemical ionization mass spectrometry.

EXAMPLE 1: Synthesis of 3-Oxacloprostenol (5)



A: Ethyl (3-chlorophenoxy)acetate (**10**)

Acetone (320 ml), 75 g (450 mmol) of ethyl bromoacetate, and 40.0 g (310 mmol) of 3-chlorophenol were mixed together, then 69.8 g (505 mmol) of potassium carbonate was added. The mixture was mechanically stirred and heated to reflux for 4 h, and after cooling to room temperature, was poured into 350 mL of ethyl acetate. To this was then cautiously added 400 mL of 1 *M* HCl, taking care to avoid excess foaming. The layers were separated and the aqueous layer was extracted with portions of ethyl acetate (3 X 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the resulting solid was recrystallized from hexane to afford 58 g (87%) of **10** as a white solid, m.p. = 39-40 °C. ^{1}H NMR δ 7.20-7.08 (m, 1 H), 6.95-6.82 (m, 2 H), 6.75-6.70 (m, 1 H), 4.53 (s, 2 H), 4.21 (q, J = 7.2 Hz, 2 H), 1.23 (t, J = 7.2 Hz, 3 H).

B: Dimethyl [3-(3-chlorophenoxy)-2-oxoprop-1-yl]phosphonate (**11**)

To 20.6 g (166 mmol, 238 mol%) of dimethyl methylphosphonate in 110 mL of THF at -78 °C was added dropwise 65 mL (162 mmol, 232 mol%) of a 2.5 *M* solution of *n*-BuLi in hexanes. After addition was complete, the mixture was stirred for an additional 1 h, after which 15.0 g (69.9 mmol) of aryloxyester **10** in 40 mL of THF was added dropwise. The reaction was stirred for 1 h and then quenched by the addition of 100 mL of saturated NH_4Cl. The mixture was poured into 200 mL of a 1/1 mixture of saturated NaCl/ethyl acetate, layers were separated, and the aqueous layer was further extracted with ethyl acetate (2 X 100 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated, to afford 20.5 g (100%) of **11** as a viscous oil. ^{1}H NMR δ 7.22 (t, J = 8.1 Hz, 1 H), 7.05-6.90 (m, 2 H), 6.85-6.78 (m, 1 H), 4.72 (s, 2 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.27 (d, J = 22.8 Hz, 2 H).

C: (3a*R*, 4*R*, 5*R*, 6a*S*)-5-(Benzoyloxy)-4-[(*E*)-4-(3-chlorophenoxy)-3-oxo-1-butenyl]-hexahydro-2*H*-cyclopenta[b]furan-2-one (**13**)

Phosphonate **11** (20.5 g, 70.0 mmol), 2.6 g (62 mmol) of LiCl, and 200 mL of THF were mixed together at 0 °C and 6.10 g (60.4 mmol) of NEt_3 was added. Aldehyde **12** (14.0 g, 51.1 mmol) dissolved in 50 mL of CH_2Cl_2 was then added dropwise. After 1 h, the reaction was poured into 200 mL of a 1/1 mixture of saturated NH_4Cl/ethyl acetate, the layers were separated, and the aqueous layer was extracted with ethyl acetate (2 X 100 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexanes, 3/2, to afford 16.2 g (72%) of **13** as a white crystalline solid, m.p. = 101.0-102.0 °C. ^{1}H NMR δ 8.0-7.9 (m, 2 H), 7.62-7.52 (m, 1 H), 7.50-7.38 (m, 2 H), 7.18 (t, J = 8.2 Hz, 1 H), 7.0-6.82 (m, 3 H), 6.75-6.70 (m, 1 H), 6.54 (d, J = 15.1 Hz, 1 H), 5.32 (q, J = 6.2 Hz, 1 H), 5.12-5.05 (m, 1 H), 4.66 (s, 2 H), 3.0-2.8 (m, 3 H), 2.7-2.2 (m, 3 H).

D: (3a*R*, 4*R*, 5*R*, 6a*S*)-5-(Benzoyloxy)-4-[(*E*)-(3*R*)-4-(3-chlorophenoxy)-3-hydroxy-1-butenyl]-hexahydro-2*H*-cyclopenta[b]furan-2-one (**14**)

To a solution of 9.70 g (22.0 mmol) of enone **13** in 60 mL of THF at -23 °C was added dropwise a solution of 11.1 g (34.6 mmol) of (-)-*B*-chlorodiisopinocampheylborane in 30 mL of THF. After 4 h, the reaction was quenched by the dropwise addition of 5 mL of methanol and then warmed to room temperature. After pouring into 200 mL of a 2/1 mixture of ethyl acetate/saturated NH_4Cl, the layers were separated, and the aqueous phase was extracted with ethyl acetate (2 X 100 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexanes, 3/2, to afford 4.7 g (48%) of **14** as a white solid, m. p. 101.0-102.5 °C. ^{1}H NMR δ 8.05-7.95 (m, 2 H), 7.62-7.40 (m, 3 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.0-6.92 (m, 1 H), 6.85 (t, J = 2.1 Hz, 1 H), 6.77-6.70 (m, 1 H), 5.85 (d of d, J = 6.2, 15.5 Hz, 1 H), 5.72 (d of d, J = 4.5, 15.5 Hz, 1 H), 5.30 (q, J = 5.8 Hz, 1 H), 5.12-5.04 (m, 1 H), 4.58-4.48 (m, 1 H), 3.92 (d of d, J = 3.5, 9.3 Hz, 1 H), 3.80 (d of d, J = 7.3, 9.4 Hz, 1 H), 2.9-2.2 (m, 8 H).

E: (3a*R*, 4*R*, 5*R*, 6a*S*)-4-[(*E*)-(3*R*)-4-(3-Chlorophenoxy)-3-(tetrahydropyran-2-yloxy)-1-butenyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[b]furan-2-one (**16**)

To a mixture of 5.1 g (11.5 mmol) of **14** in 200 mL of methanol was added 1.7 g (12 mmol) of K_2CO_3. After 1 h, the mixture was poured into 100 mL of 0.5 *M* HCl and extracted with ethyl acetate (3 X 100 mL). The combined organic layers were washed successively with water (2 X 100 mL) and saturated NaCl (2 X 100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to afford 4.85 g of crude diol **15**, which was used in the next step without further purification.

To a mixture of 4.85 g of crude **15** and 2.4 g (28 mmol) of 3,4-dihydro-2*H*-pyran in 75 mL of CH_2Cl_2 at 0 °C was added 370 mg (1.9 mmol) of *p*-toluenesulfonic acid monohydrate. After stirring for 45 min, the reaction was poured into 40 mL of saturated $NaHCO_3$, layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 X 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel eluting with 40% ethyl acetate in hexanes, to afford 6.0 g (100%) of **16** as an oil. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.25-7.14 (m, 1 H), 6.95-6.87 (m, 2 H), 6.83-6.72 (m, 1 H), 5.8-5.4 (m, 4 H), 5.1-4.8 (m, 2 H).

F: (13*E*)-(9*S*, 11*R*, 15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4,5,6,17,18,19,20-nonanor-9-triethylsilyloxy-13-prostenol Triethylsilyl Ether (**18**)

To a suspension of 400 mg (10.5 mmol) of lithium aluminum hydride in 20 mL of THF at 0 °C was added dropwise a solution of 4.5 g (8.8 mmol) of lactone **16** in 20 mL of THF. After 1 h at 0 °C the mixture was cautiously poured into 100 mL of a 1/1 mixture of ice-cold saturated NH_4Cl/ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 X 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 4.5 g (100%) of diol **17** which was used in the next step without further purification.

Triethylsilyl chloride (3.0 g, 20 mmol) was added to a mixture of 4.5 g (8.8 mmol) of crude **17**, 40 mL of DMF, 1.85 g (27.0 mmol) of imidazole, and 310 mg (2.5 mmol) of 4-(dimethylamino)pyridine. After 2 h, the reaction was poured into 100 mL of a 1/1 mixture of ethyl acetate/saturated NH_4Cl, layers were separated, and the aqueous layer was extracted with ethyl acetate (2 X 25 mL). The combined organic layers were washed with water (3 X 25 mL), dried over $MgSO_4$, and concentrated. The residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to afford 5.2 g (80%) of **18**. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.22-7.12 (m, 1 H), 6.95-6.88 (m, 2 H), 6.83-6.71 (m, 1 H), 5.8-5.4 (m, 4 H), 5.1-4.8 (m, 2 H), 1.0-0.85 (m, 18 H), 0.7-0.5 (m, 12 H).

G: (13*E*)-(*9S*, 11*R*, 15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-2,3,4,5,6,17,18,19,20-nonanor-9-triethylsilyloxy-13-prostenal (**19**)

To a mixture of 1.6 g (12.6 mmol) of oxalyl chloride and 15 mL of CH_2Cl_2 at -78 °C was added dropwise a solution of 1.54 g (19.7 mmol) of DMSO in 2 mL of CH_2Cl_2 . After 10 min, 4.6 g (6.2 mmol) of bissilane **18** in 8 mL of CH_2Cl_2 was added dropwise. After 95 min, 3.0 g (30 mmol) of NEt_3 was added. The mixture was then warmed to room temperature and poured into 70 mL of saturated NH_4Cl. The solution was extracted with of CH_2Cl_2 (3 X 70 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to afford 2.06 g (53%) of **19** as well as 1.5 g (26%) recovered **18**. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 9.78 (t, J = 1.4 Hz, 1 H), 7.22-7.12 (m, 1 H), 6.95-6.88 (m, 2 H), 6.83-6.71 (m, 1 H), 5.8-5.4 (m, 4 H) 5.1-4.8 (m, 2 H), 1.0-0.85 (m, 18 H), 0.7-0.5 (m, 12 H).

H: (5*Z*, 13*E*)-(9*S*, 11*R*, 15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chloro-phenoxy)-2,3,4,17,18,19,20-heptanor-9-triethylsilyloxy-5,13-prostadienoic Acid Methyl Ester (**21**)

To a solution of 1.35 g (4.24 mmol) of phosphonate **20** and 2.60 g (9.84 mmol) of 18-crown-6 in 20 mL of THF at -78 °C was added dropwise 6.9 mL (3.45 mmol) of a 0.5 *M* solution of potassium hexamethyldisilazane in toluene. After stirring for 15 min, a solution of 1.65 g (2.64 mmol) of aldehyde **19** in 20 mL of THF was added dropwise. One hour later, the mixture was poured into 100 mL of saturated NH_4Cl/ethyl acetate, 1/1, layers were separated, and the aqueous layer was extracted with ethyl acetate (3 X 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated and the residue was chromatographed on silica gel eluting with 20% ethyl acetate in hexane to afford 1.135 g (63%) of **21**. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.22-7.11 (m, 1 H), 6.97-6.86 (m, 2 H), 6.85-6.75 (m, 1 H), 6.4-6.2 (m, 1 H), 5.8-5.32 (m, 3 H), 3.66 (s, 3 H).

I: (5*Z*, 13*E*)-(9*S*, 11*R*, 15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chloro-phenoxy)-2,3,4,17,18,19,20-heptanor-9-triethylsilyloxy-5,13-prostadien-1-ol (**22**)

To a solution of 850 mg (1.25 mmol) of ester **21** in 10 mL of THF at 0 °C was added 2.4 mL (3.6 mmol) of a 1.5 *M* solution of diisobutylaluminum hydride in toluene. After 1 h, the mixture was poured into 20 mL of saturated NH_4Cl and was extracted with ethyl acetate (3 X 20 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated down to 800 mg (98%) of **22** as an oil. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.25-7.15 (m, 1 H), 6.97-6.90 (m, 2 H), 6.86-6.75 (m, 1 H), 5.81-5.41 (m, 4 H).

J: (5*Z*, 13*E*)-(9*S*, 11*R*, 15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chloro-phenoxy)-3-oxa-17,18,19,20-tetranor-9-triethylsilyloxy-5,13-prostadienoic Acid Isopropyl Ester (**23**)

To a solution of 415 mg (6.37 mmol) of alcohol **22** in 4 mL of THF at -78 °C was added dropwise 0.35 mL (0.87 mol) of a 2.5 *M* solution of *n*-BuLi in hexane. After 15 min, this solution was transferred *via* syringe to a -78 °C solution of 195

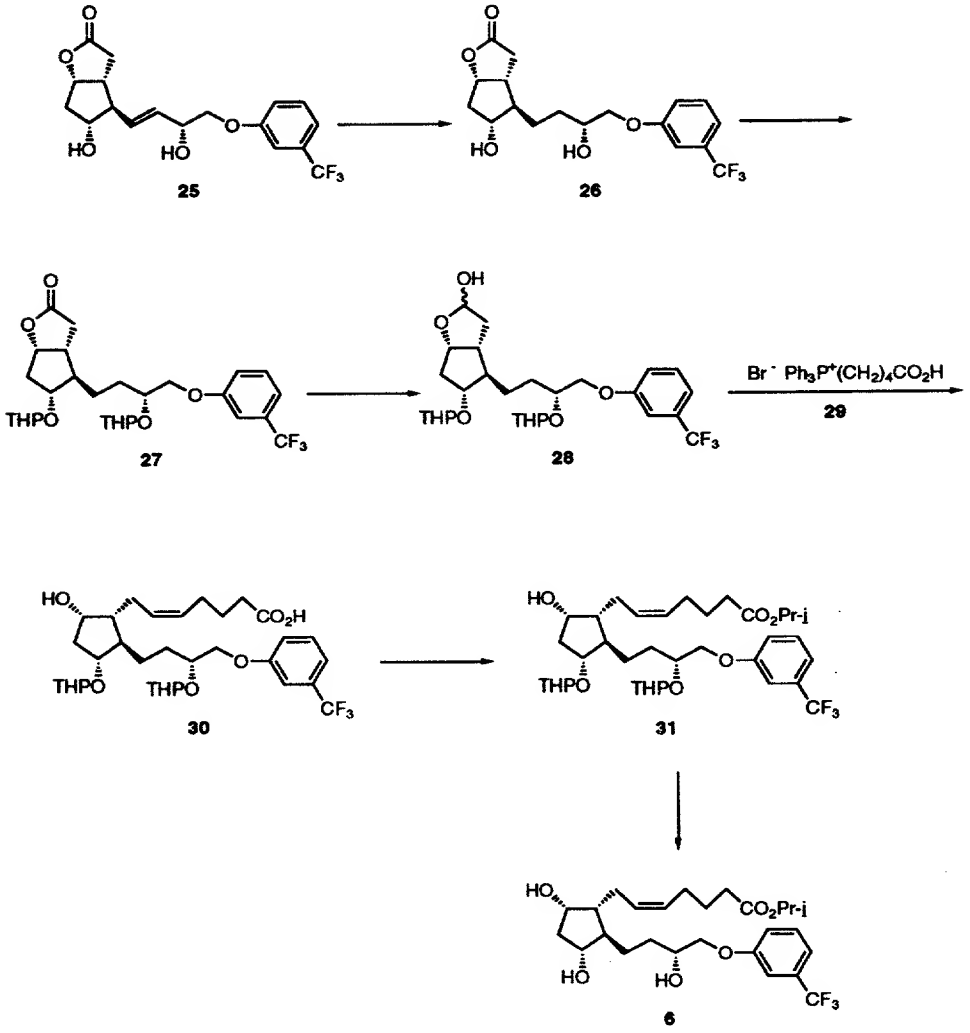
mg (1.08 mmol) of isopropyl bromoacetate in 2 mL of THF. The mixture was kept at -78 °C for 40 min, warmed to room temperature overnight, and then poured into 20 mL of a 1/1 mixture of saturated NH_4Cl/ethyl acetate. Layers were separated, and the aqueous layer was extracted with ethyl acetate (2 X 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (20% ethyl acetate in hexane) to afford 242 mg (53%) of **23** as an oil. ^1H NMR ($CDCl_3$) δ (characteristic peaks only) 7.24-7.15 (m, 1 H), 6.97-6.90 (m, 2 H), 6.86-6.75 (m, 1 H), 5.81-5.41 (m, 4 H), 1.57 (d, J = 5.7 Hz, 6 H).

K: (5*Z*, 13*E*)-(9*S*, 11*R*, 15*R*)-16-(3-Chlorophenoxy)-3-oxa-17,18,19,20-tetranor-9,11,15-trihydroxy-5,13-prostadienoic Acid Isopropyl Ester (**5**)

To a solution of 230 mg (0.32 mmol) of silane **23** in 5 mL of THF at room temperature was added 0.33 mL (0.33 mmol) of a 1 *M* solution of Bu_4NF in THF. After 20 min, the reaction was poured into 4 mL of saturated NH_4Cl and was extracted with ethyl acetate (4 X 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (ethyl acetate/hexane, 1/1), to afford 126 mg (65%) of desilylated compound **24**.

To 120 mg of **24** in 5 mL of methanol was added 0.4 mL of 2 *M* HCl. After 1 h, the mixture was added to 3 mL of saturated $NaHCO_3$, and the resulting mixture was extracted with ethyl acetate (3 X 8 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated. The resulting residue was then chromatographed on silica gel eluting with ethyl acetate to afford 54 mg (56%) of **5**. ^{13}C NMR ($CDCl_3$) δ 169.92 (C), 159.26 (C), 135,13 (CH), 134.95 (CH), 134.81 (C), 124.93 (CH), 121.22 (CH), 115.06 (CH), 113.08 (CH), 77.75 (CH), 72.02 (CH), 71.94 (CH_2), 70.76 (CH_2), 68.77 (CH), 67.78 (CH_2), 66.50 (CH_2), 55.46 (CH), 49.93 (CH), 42.47 (CH_2), 25.85 (CH_2), 21.75 (CH_3). CI MS, *m/z* calcd. for $C_{24}H_{34}O_7Cl_1$ (MH^+), 469.1993, found 469.1993.

EXAMPLE 2: Synthesis of 13,14-Dihydrofluprostenol Isopropyl Ester



A: (3a*R*, 4*R*, 5*R*, 6a*S*)-5-Hydroxy-4-[(3*R*)-4-(3-trifluoromethylphenoxy)-3-hydroxy-1-butyl]-hexahydro-2*H*-cyclopenta[b]furan-2-one (**26**)

A mixture of 1.2 g (3.2 mmol) of diol **25** (for synthesis of diol **25**, see U.S. Patent 4,321,275) and 0.05 g of 10% (wt/wt) Pd/C in 20 mL of methanol was hydrogenated at 30 psi for 1.5 hours. After filtration through a short pad of Celite® concentration afforded 1.2 g (100%)of **26** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 7.44 (m, 2 H), 7.12 (m, 2 H), 4.95 (dt, 1 H), 4.15-3.80 (m, 4 H), 2.82 (dd, J = 10.8, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1-1.3 (m, 6 H).

B: (3a*R*, 4*R*, 5*R*, 6a*S*)-5-(Tetrahydropyran-2-yloxy)-4-[(3*R*)-4-(3-trifluoromethylphenoxy)-3- (tetrahydropyran-2-yloxy)-1-butyl]-hexahydro-2*H*-cyclopenta[b]furan-2-one (**27**)

A mixture of 1.2 g (3.2 mmol) of diol **26** and 0.05 g of *p*-toluenesulfonic acid monohydrate in 100 mL of CH_2Cl_2 at 0 °C was treated with 3,4-dihydro-2*H*-pyran (1.1 ml, 12 mmol) and the solution was stirred for 2 h at 0 °C. After pouring into saturated $NaHCO_3$, phases were separated and the organic layer was dried over $MgSO_4$, filtered, concentrated, and purified by chromatography on silica gel (1/1, hexanes/ EtOAc) to afford 1.1 g of **27** as a clear, colorless oil. ^{1}H NMR ($CDCl_3$) δ 8.04 (dd, J = 7.0, 1.6, 1 H), 7.44 (m, 2 H), 7.12 (m, 1 H), 4.95 (dt, 1 H), 4.8 (m, 1 H), 4.7 (m, 2 H), 4.15-3.80 (m, 4 H), 3.5 (m, 2 H), 2.82 (dd, J = 10.8, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1-1.3 (m, 6 H).

C: (5*Z*)-(9*S*, 11*R*, 15 *R*)-11,15-*Bis*(tetrahydropyran-2-yloxy)-9-hydroxy-17,18,19,20-tetranor-16-(3-trifluoromethylphenoxy)-5-prostenoic Acid Isopropyl Ester (**31**)

To a solution of 2.1 g (3.9 mmol) of **27** in 100 mL of THF at -78 °C was added 3.9 mL (5.8 mmol) of a 1.5 M solution of diisobutyaluminum hydride in toluene. The solution was stirred for 2 h, then quenched by the sequential addition of 0.4 mL of isopropanol at -78 °C followed by 0.4 mL of water at 23 °C. Volatiles

were removed under reduced pressure and the aqueous solution was extracted with Et_2O/EtOAc (1/1). Organic extracts were dried over $MgSO_4$, filtered, and concentrated to furnish 1.9 g of lactol **28**.

To a 250 mL 3-necked round bottom flask equipped with a mechanical stirrer and a thermometer were added anhydrous DMSO (100 mL) and NaH (80% dispersion in mineral oil; 0.48 g, 16 mmol). The mixture was heated to 75 °C (internal) for 30 min, after which it was allowed to cool to room temperature for 1 h. Phosphonium bromide **29** (3.5 g, 8 mmol) was then added. After stirring for 30 minutes, 1.9 g (3.5 mmol) of lactol **28** in 50 mL of DMSO was added, and the resulting solution was heated to 50 °C for 2 h and then brought to room temperature for 16 h. The solution was poured into 100 mL of water and approximately 2 mL of 50% NaOH added. The aqueous phase was extracted with ether (3 X 100 mL), then made acidic (pH = 5.5) by the addition of a 10% citric acid solution, and extracted with Et_2O/hexanes, 2/1 (3 X 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford 1.9 g of **30** as a colorless oil.

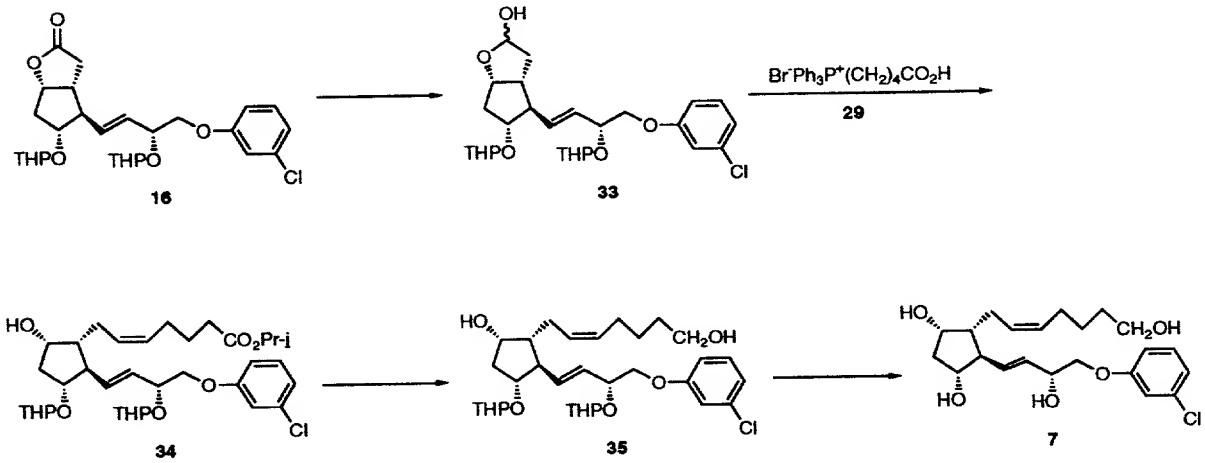
To 1.9 g of carboxylic acid **30** dissolved in 10 mL acetone was added 0.95 g (6.0 mmol) of DBU and 1.0 g (6.1 mmol) of isopropyl iodide at 23 °C. After 16 h, the solution was poured into 100 mL of water and extracted with 100 mL of EtOAc. The organic extract was dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (3/2, hexanes/EtOAc) to afford 1.9 g of isopropyl ester **31** as a colorless oil. ^1H NMR ($CDCl_3$) δ 7.44 (t, 1 H), 7.12 (d, 1 H), 7.12 (dd, 2 H), 5.5-5.3 (m, 2 H), 4.99 (heptet, 1 H), 4.15-3.80 (m, 4 H), 2.82 (dd, J = 10.8, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1-1.3 (m, 24 H), 1.23 (s, 3 H), 1.20 (s, 3 H).

D: (5*Z*)-(9*S*, 11*R*, 15*R*)-17,18,19,20-Tetranor-16-(3-trifluoromethylphenoxy)-9,11,15-trihydroxy-5-prostenoic Acid Isopropyl Ester (**6**)

Ester **31** (1.9 g, 2.8 mmol) was dissolved in 14 mL of a mixture of AcOH/THF/H_2O (4/2/1) and the solution was heated to 50 °C for 1 h, allowed to cool to 23 °C, poured into a saturated solution of $NaHCO_3$, and extracted with Et_2O

(2 X 100 mL) and EtOAc (100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (1/1, hexanes/EtOAc) to furnish 0.5 g of triol **6** as a clear, colorless oil. ^1H NMR ($CDCl_3$) δ 7.44 (t, J = 7.8, 1 H), 7.12 (dd, J = 7.8, 2.0, 1 H), 7.12 (ddd, J = 15.6, 7.2, 2.0, 2 H), 5.5-5.3 (m, 2 H), 4.99 (heptet, J = 6.3, 1 H), 4.15-3.80 (m, 4 H), 3.2 (d, 1 H), 2.95 (s, 1 H), 2.82 (dd, J = 10.8, 1 H), 2.75 (d, J = 5.9, 1 H), 2.55 (m, 2 H), 2.3 (m, 1 H), 2.1-1.3 (m, 24 H), 1.23 (s, 3 H), 1.20 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 173.5, 158.7, 132.1, 131.5, 130.0, 129.5, 129.2, 123.3, 120.8, 117.7, 117.6, 111.4, 111.4, 78.6, 74.4, 72.4, 69.9, 67.6, 52.6, 51.7, 42.5, 34.0, 31.5, 29.4, 26.8, 26.6, 24.9, 21.7.

EXAMPLE 3: Synthesis of Cloprostenol-1-ol (7)



A: (5*Z*, 13*E*)-(9*S*, 11*R*, 15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-9-hydroxy-17,18,19,20-tetranor-5,13-prostadienoic Acid Isopropyl Ester (**34**)

A 1.5 *M* solution of diisobutylaluminum hydride in toluene (10 mL, 15 mmol) was added dropwise to a solution of 5.8 g (11.4 mmol) of lactone **16** in 55 mL of THF at -78 °C. After 1 h, 10 mL of methanol was added dropwise, and the mixture

was stirred for 10 min at -78 °C before being warmed to room temperature. The mixture was then poured into 100 mL of a 1/1 solution of saturated aqueous potassium sodium tartrate/ethyl acetate and stirred. After separating layers, the aqueous phase was extracted with ethyl acetate (2 X 40 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (3/2, ethyl acetate/hexane), to afford 4.4 g (76%) of lactol **33**, which was used immediately in the next step.

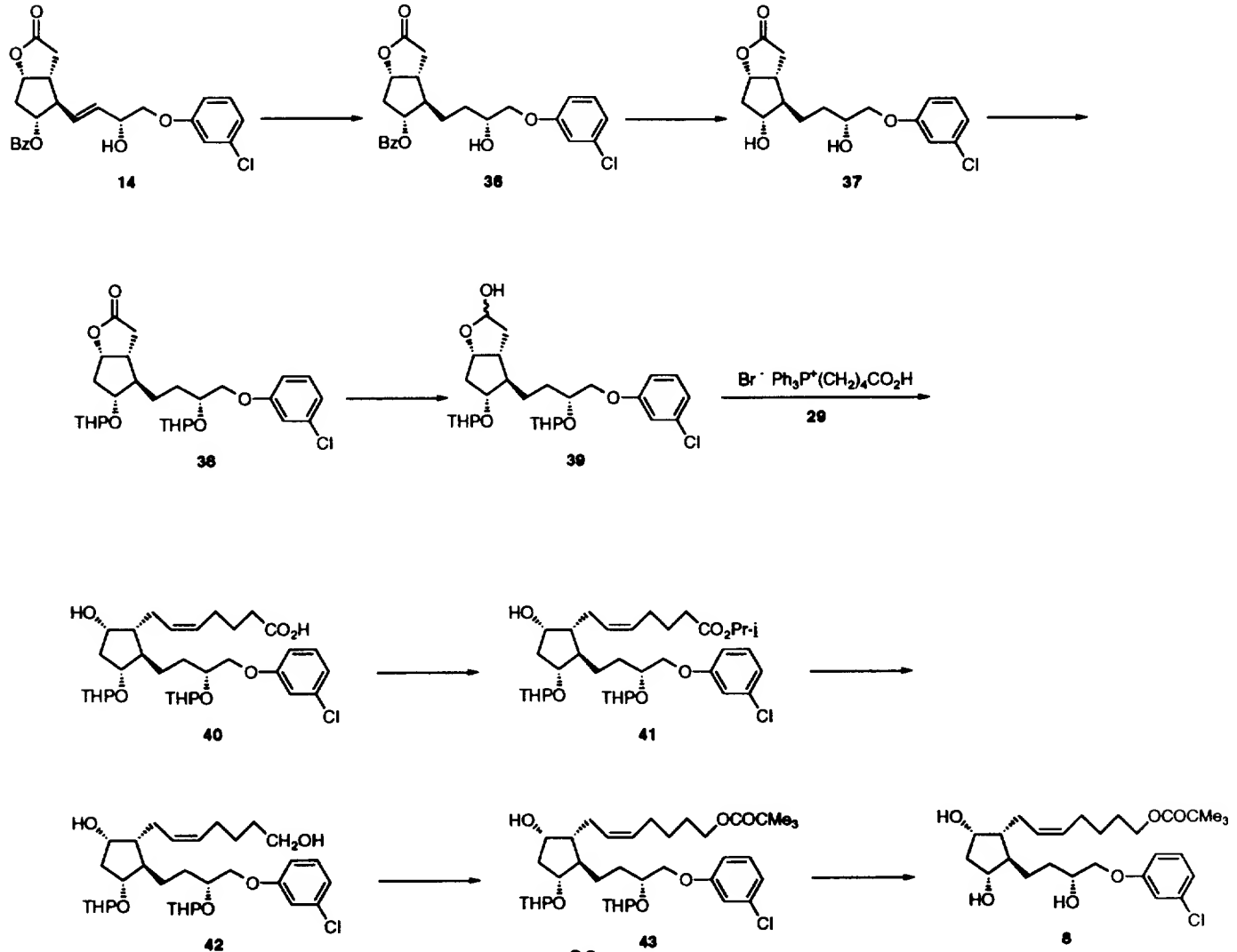
A 1 *M* solution of potassium *t*-butoxide in THF (50.0 ml) was added dropwise to 12.1 g (27.3 mmol) of phosphonium salt **29** in 100 mL of THF at 0 °C. After 30 min, a solution of 4.4 g (8.6 mmol) of lactol **33** in 20 mL of THF was added dropwise, and the mixture was stirred at room temperature overnight. The solution was then poured into 150 mL of a 1/1 mixture of ethyl acetate/saturated NH_4Cl. Layers were separated and the aqueous layer was extracted with ethyl acetate (2 X 100 mL). Combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was redissolved in 80 mL of acetone. To this was added 6.5 g (45 mmol) of DBU followed by 7.3 g (43 mmol) of isopropyl iodide. After stirring overnight, the reaction was poured into 100 mL of a 1/1 mixture of ethyl acetate/saturated NH_4Cl. Layers were then separated and the aqueous phase was further extracted with ethyl acetate (2 X 100 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (40% ethyl acetate in hexane) to afford 2.92 g (53% from lactone **16**) of ester **34**.

B: (5*Z*, 13*E*)-(9*S*, 11*R*, 15*R*)-16-(3-Chlorophenoxy)-17,18,19,20-tetranor-9,11,15-trihydroxy-5,13-prostadienol (**7**)

A solution of 500 mg (0.79 mmol) of **34** in 10 mL of THF was added dropwise to 61 mg (1.60 mmol) of lithium aluminum hydride in 20 mL of THF at 0 °C. After 40 min, the reaction was carefully poured into 15 mL of saturated NH_4Cl, and the mixture was then extracted with ethyl acetate (3 X 40 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 500 mg of crude **35**.

To a solution of 500 mg of **35** in 20 mL of methanol was added 0.5 mL of 2 *M* HCl. After 1 h, the reaction was quenched with 20 mL of saturated $NaHCO_3$ and the mixture was extracted with ethyl acetate (4 X 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Silica gel chromatography (EtOAc) provided 101 mg (31% from **34**) of **7**. ^{13}C NMR ($CDCl_3$) δ 159.27 (C), 135.44 (CH), 134.82 (C), 130.64 (CH), 130.26 (CH), 128.23 (CH), 121.25 (CH), 115.07 (CH), 113.08 (CH), 77.35 (CH), 72.35 (CH), 71.90 (CH_2), 70.89 (CH), 62.22 (CH_2), 55.40 (CH), 49.87 (CH), 42.79 (CH_2), 31.83 (CH_2), 26.77 (CH_2), 25.60 (CH_2), 25.33 (CH_2). CI MS *m/z* calcd for $C_{22}H_{32}O_5Cl_1$ (MH^+) 411.1938, found 411.1938.

EXAMPLE 4: Synthesis of 13,14-Dihydrocloprostenol-1-ol Pivaloate (8)



A: (3a*R*, 4*R*, 5*R*, 6a*S*)-4-[(3*R*)-4-(3-Chlorophenoxy)-3-hydroxybutyl]-5-hydroxy-hexahydro-2*H*-cyclopenta[b]furan-2-one (**37**):

A mixture of 2.4 g (5.4 mmol) of **14** and 250 mg of 10% (wt/wt) Pd/C in 35 mL of ethyl acetate was hydrogenated at 40 psi for 1 h. After filtration through a short pad of Celite®, the filtrate was evaporated down to 2.3 g (100%) of hydrogenated product **36**.

The crude benzoate **36** was dissolved in 25 mL of methanol, and 610 mg (4.4 mmol) of K_2CO_3 was added. After 3.5 h, the mixture was poured into 100 mL of water/ethyl acetate (1/1). Layers were separated, and the aqueous phase was further extracted with ethyl acetate (2 X 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Silica gel chromatography (EtoAc) provided 1.50 g (82%) of **37** as a white solid, m.p. = 102.0-103.5 °C. ^{1}H NMR δ 7.22 (t, J = 8.2 Hz, 1 H), 7.0-6.94 (m, 1 H), 6.91-6.88 (t, J = 2.1 Hz, 1 H), 6.83-6.77 (m, 1 H), 4.97 (dt, J = 3.0, 8.3 Hz, 1 H), 4.12-3.91 (m, 3 H), 3.82 (dd, J = 7.4, 9.0 Hz, 1 H), 2.85 (dd, J = 8.0, 16.5 Hz, 1 H), 2.6-1.4 (m, 11 H).

B: (3a*R*, 4*R*, 5*R*, 6a*S*)-4-[(3*R*)-4-(3-Chlorophenoxy)-3-(tetrahydropyran-2-yloxy)butyl]-5-(tetrahydropyran-2-yloxy)-hexahydro-2*H*-cyclopenta[b]furan-2-one (**38**)

Diol **37** (3.4 g, 10 mmol) and 2.2 g (26 mmol) of 3,4-dihydro-2*H*-pyran were dissolved in 80 mL of CH_2Cl_2, and 240 mg (1.3 mmol) of *p*-toluenesulfonic acid monohydrate was added at 0 °C. After 1 h, the reaction was poured into 50 mL of saturated $NaHCO_3$ and the mixture was extracted with CH_2Cl_2 (3 X 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (hexane/ethyl acetate, 1/1) to afford 4.5 g (87%) of bis-THP ether **38**.

C: (5*Z*)-(9*S*, 11*R*, 15*R*)-11,15-Bis(tetrahydropyran-2-yloxy)-16-(3-chlorophenoxy)-9-hydroxy-17,18,19,20-tetranor-5-prostenoic Acid Isopropyl Ester (**41**)

A 1.5 *M* solution of diisobutylaluminum hydride in toluene (1.8 mL, 2.7 mmol) was added to the solution 1.05 g (2.06 mmol) of **38** in 10 mL of THF at -78 °C. After 1 h, 4 mL of methanol was added and the mixture was warmed to 25 °C, then

poured into 40 mL of ethyl acetate/saturated aqueous potassium sodium tartrate (1/1). Layers were separated and the aqueous phase was further extracted with ethyl acetate (3 X 30 mL). The combined organic layers were then dried over $MgSO_4$, filtered, concentrated, and the residue was chromatographed on silica gel (ethyl acetate) to afford 740 mg (70%) of lactol **39**.

A 1.5 *M* solution of potassium *t*-butoxide in THF (8.6 mL, 8.6 mmol) was added dropwise to a mixture of 15 mL of THF and 1.92 g (4.33 mmol) of phosphonium salt **29** at 0 °C. After stirring for 1 h, a solution of 740 mg (1.45 mmol) of lactol **39** in 5 mL of THF was added dropwise, and the reaction was allowed to warm to 25 °C overnight. The mixture was then poured into 100 mL of ethyl acetate/saturated NH_4Cl (1/1). Layers were separated, and the aqueous phase was further extracted with ethyl acetate (2 X 70 mL). Combined organic layers were dried over $MgSO_4$, filtered, and concentrated to afford 1.6 g of crude acid **40**.

Crude acid **40** (1.6 g) was dissolved in 11 mL of acetone and cooled to 0 °C, then 850 mg (5.6 mmol) of DBU was added dropwise to the solution. The resulting mixture was stirred for 15 min at 0 °C and 30 min at 25 °C, after which 850 mg (5.0 mmol) of isopropyl iodide was added. The reaction was stirred overnight and poured into 100 mL of ethyl acetate/saturated NH_4Cl (1/1). Layers were separated, and the aqueous phase was further extracted with ethyl acetate (2 X 50 mL). Combined organic layers were dried over $MgSO_4$, filtered and concentrated. The resulting residue was purified by silica gel chromatography (ethyl acetate/hexanes, 3/2) to afford 560 mg (61% from lactol **39**) of isopropyl ester **41**.

D: (5*Z*)-(9*S*, 11*R*, 15*R*)-16-(3-Chlorophenoxy)-17,18,19,20-tetranor-9,11,15-trihydroxy-5-prostenol Pivaloate (**8**)

A solution of 400 mg (0.63 mmol) of **41** in 5 mL of THF was added dropwise to a suspension of 35 mg (0.92 mmol) of lithium aluminum hydride in 5 mL of THF at 0 °C. After 2 h, the reaction was poured into 50 mL of a 1/1 mixture of ethyl acetate/saturated $NaHCO_3$. The layers were then separated, and the aqueous phase was extracted with ethyl acetate (2 X 2 mL). Combined organic layers were

dried over $MgSO_4$, filtered, and concentrated. The resulting residue was purified by silica gel chromatography (ethyl acetate) to afford 350 mg (95%) of diol **42**.

Pivaloyl chloride (90 mg, 0.75 mmol) was added to a mixture of 350 mg (0.60 mmol) of **42**, 60 mg (0.76 mmol) of pyridine, 22 mg (0.18 mmol) of 4-(dimethylamino)pyridine, and 7 mL of CH_2Cl_2. After 1.5 h, the mixture was poured into 30 mL of saturated NH_4Cl/ethyl acetate (1/1). Layers were then separated and the aqueous phase was extracted with ethyl acetate (2 X 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (ethyl acetate/hexane, 3/2) to afford 370 mg (93%) of pivaloate **43**.

Water (approximately 10 drops) and concentrated HCl (approximately 3 drops) were added to a solution of 370 mg (0.56 mmol) of **43** in 5 mL of methanol. After stirring overnight, the reaction was quenched by the addition of 20 mL of saturated $NaHCO_3$, and the mixture was extracted with ethyl acetate (3 X 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on silica gel (ethyl acetate/hexane, 3/2), to afford 165 mg (59%) of triol **8**. ^{13}C NMR ($CDCl_3$) δ 178.77 (C), 159.27 (C), 134.80 (C), 130.20 (CH), 128.62 (CH), 121.19 (CH), 114.97 (CH), 112.97 (CH), 78.50 (CH), 74.46 (CH), 72.31 (CH_2), 69.86 (CH), 64.16 (CH_2), 52.53 (CH), 51.67 (CH), 42.50 (CH_2), 31.51 (CH_2), 29.40 (CH_2), 28.10 (CH_2), 27.12 (CH_3), 26.77 (CH_2), 26.65 (CH_2), 25.77 (CH_2). CI MS, *m/z* calcd for $C_{27}H_{41}O_6Cl_1$ (MH^+), 497.2670, found 497.2656

EXAMPLE 5

$PGF_{2\alpha}$ analogues are known to contract the iris sphincter of cats and this assay is a generally accepted reference for activity. For this reason, the pupil diameter of cats may be used to define the activity of $PGF_{2\alpha}$ analogues and, as demonstrated by Stjernschantz and Resul (Drugs Future, 17:691-704 (1992)), predict the IOP-lowering potency.

Compounds of the present invention were therefore screened for pupillary constriction in the cat. Data for compounds **6, 7,** and **8** are presented in Table 2, below. The response is quantitated as Area $_{1\text{-}5}$ values (area under the pupil diameter versus time curve from 1-5 hours), and the equivalent response dose (ED_5) is estimated from its dose response relationship.

Table 2: Cat Pupil Diameter Response

Compound	ED_5 (µg)
$PGF_{2\alpha}$ Isopropyl Ester	0.02
Cloprostenol Isopropyl Ester	0.01
6	0.2
7	0.02
8	0.06

Discussion:

The two standard compounds, $PGF_{2\alpha}$ isopropyl ester and cloprostenol isopropyl ester, produced marked change in cat pupillary diameter, displaying ED_5 values of 0.02 and 0.01 µg, respectively. Compound **7** (cloprostenol-1-ol) and compound **8** (13,14-dihydrocloprostenol-1-ol pivaloate), displayed nearly equivalent potency. 13,14-Dihydrofluprostenol isopropyl ester (compound **6**) was approximately one order of magnitude less potent, with an ED_5 of 0.2 µg.

EXAMPLE 6

In the study presented below, compound **6** (Table 1, above) was tested for IOP-lowering effect in cynomolgus monkey eyes.

The right eyes of the cynomolgus monkeys used in this study were previously given laser trabeculoplasty to induce ocular hypertension in the lasered eye. Animals had been trained to sit in restraint chairs and conditioned to accept experimental procedures without chemical restraint. IOP was determined with a

pneumatonometer after light corneal anesthesia with dilute proparacaine. The test protocol included a five-dose treatment regimen because of the typical delayed response to prostaglandins. The designated test formulations were administered to the lasered right eyes, and the normal left eyes remained untreated, although IOP measurements were taken. Baseline IOP values were determined prior to treatment with the test formulation, and then IOP was determined from 1 to 7 hours after the first dose, 16 hours after the fourth dose, and 1 to 4 hours after the fifth dose.

The equivalent response dose (ED_{20}) is estimated from the dose response relationship to be the dose producing a 20% peak reduction in IOP.

Table 3: Monkey IOP Response

Compound	ED_{20} (µg)
$PGF_{2\alpha}$ Isopropyl Ester	0.4
6	0.3

Discussion:

As can be seen in Table 3, compound **6**, the 13,14-dihydro analogue of fluprostenol was quite potent in the monkey IOP model, producing a 20% reduction at 0.3 µg. This was even more potent than the standard compound, $PGF_{2\alpha}$ isopropyl ester.

EXAMPLE 7

The following Formulations 1-4 are representative pharmaceutical compositions of the invention for topical use in lowering of intraocular pressure. Each of Formulations 1 through 4 may be formulated in accordance with procedures known to those skilled in the art.

FORMULATION 1

Ingredient	Amount (wt%)
Compound **5** (Table 1)	0.002
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.3
Sodium chloride	0.77
Potassium chloride	0.12
Disodium EDTA	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.2 - 7.5
Purified water	q.s. to 100%

FORMULATION 2

Ingredient	Amount (wt%)
Compound **6** (Table 1)	0.01
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA	0.01
Benzalkonium chloride	0.02
Polysorbate 80	0.15
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

FORMULATION 3

Ingredient	Amount (wt%)
Compound **7** (Table 1)	0.001
Dextran 70	0.1
Hydroxypropyl methylcellulose	0.5
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA	0.05
Benzalkonium chloride	0.01
NaOH and/or HCl	pH 7.3 - 7.4
Purified water	q.s. to 100%

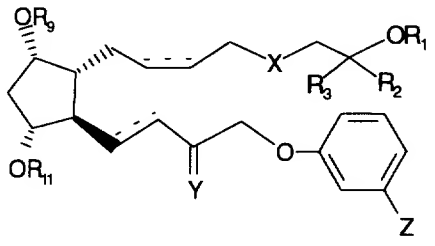
FORMULATION 4

Ingredient	Amount (wt%)
Compound **8** (Table 1)	0.003
Monobasic sodium phosphate	0.05
Dibasic sodium phosphate (anhydrous)	0.15
Sodium chloride	0.75
Disodium EDTA	0.05
Benzalkonium chloride	0.01
HCl and/or NaOH	pH 7.3 - 7.4
Purified water	q.s. to 100%

The invention has been described by reference to certain preferred embodiments; however, it should be understood that it may be embodied in other specific forms or variations thereof without departing from its spirit or essential characteristics. The embodiments described above are therefore considered to be illustrative in all respects and not restrictive, the scope of the invention being indicated by the appended claims rather than by the foregoing description.

What is Claimed is:

1. A method of treating glaucoma and ocular hypertension which comprises topically administering to the affected eye a therapeutically effective amount of a compound of formula:



(IV)

wherein:

R_1 = H; C_1-C_{12} straight-chain or branched alkyl; C_1-C_{12} straight-chain or branched acyl; C_3-C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 = H, or C_1-C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X = O, S, or CH_2;

---- represents any combination of a single bond, or a *cis* or *trans* double bond for the alpha (upper) chain; and a single bond or *trans* double bond for the omega (lower) chain;

R_9 = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

R_{11} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

Y = O; or H and OR_{15} in either configuration wherein R_{15} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl; and

Z = Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$-C_{12} straight-chain or branched acyl; and when $R_2 = R_3$ = H, then $R_1 \neq$ a cationic salt moiety.

2. The method of claim 1, wherein: $R_2 = R_3 = H$, or R_2 and R_3 taken together represent O; X = O or CH_2; $R_9 = R_{11} = H$; Y = H and OR_{15}; and $R_{15} = H$.

3. The method of claim 2, wherein: $R_1 = H$ or C_1-C_{12} straight chain or branched alkyl; and R_2 and R_3 taken together represent O.

4. The method of claim 3, wherein the compound of formula (IV) is selected from the group consisting of 3-oxacloprostenol, 13,14-dihydrofluprostenol, and their pharmaceutically acceptable esters and salts.

5. The method of claim 2, wherein: $R_1 = H$ or C_1-C_{12} straight chain or branched acyl; and $R_2 = R_3 = H$.

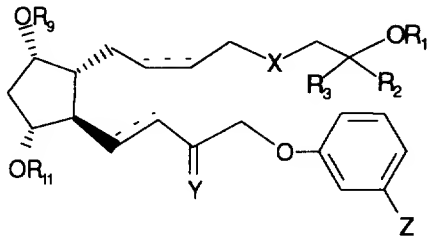
6. The method of claim 5, wherein the compound of formula (IV) is selected from the group consisting of cloprostenol-1-ol and 13,14-dihydrocloprostenol pivaloate.

7. The method of claim 1, wherein between about 0.01 and about 1000 µg/eye of the compound is administered.

8. The method of claim 7, wherein between about 0.1 and about 100 µg/eye of the compound is administered.

9. The method of claim 8, wherein between about 0.1 and about 10 µg/eye of the compound is administered.

10. A topical ophthalmic composition for the treatment of glaucoma and ocular hypertension comprising a therapeutically effective amount of a compound of formula:



(IV)

wherein:

R_1 = H; C_1-C_{12} straight-chain or branched alkyl; C_1-C_{12} straight-chain or branched acyl; C_3-C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 = H, or C_1-C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X = O, S, or CH_2;

---- represents any combination of a single bond, or a *cis* or *trans* double bond for the alpha (upper) chain; and a single bond or *trans* double bond for the omega (lower) chain;

R_9 = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

R_{11} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

Y = O; or H and OR_{15} in either configuration wherein R_{15} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl; and

Z = Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$-C_{12} straight-chain or branched acyl; and when $R_2 = R_3$ = H, then $R_1 \neq$ a cationic salt moiety.

11. The composition of claim 10, wherein: $R_2 = R_3$ = H, or R_2 and R_3 taken together represent O; X = O or CH_2; $R_9 = R_{11}$ = H; Y = H and OR_{15}; and R_{15} = H.

12. The composition of claim 11, wherein: R_1 = H or C_1-C_{12} straight chain or branched alkyl; and R_2 and R_3 taken together represent O.

13. The composition of claim 12, wherein the compound of formula (IV) is selected from the group consisting of 3-oxacloprostenol, 13,14-dihydrofluprostenol, and their pharmaceutically acceptable esters and salts.

14. The composition of claim 11, wherein: R_1 = H or C_1-C_{12} straight chain or branched acyl; and R_2 = R_3 = H.

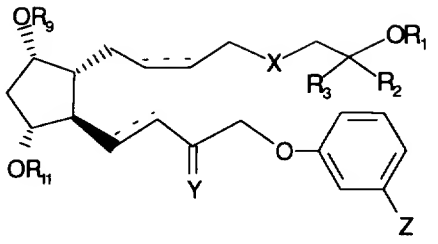
15. The composition of claim 14, wherein the compound of formula (IV) is selected from the group consisting of cloprostenol-1-ol and 13,14-dihydrocloprostenol pivaloate.

16. The composition of claim 10, wherein the concentration of the compound of formula (IV) is between about 0.00003 and about 3 wt%.

17. The composition of claim 16, wherein the concentration of the compound of formula (IV) is between about 0.0003 and about 0.3 wt%.

18. The composition of claim 17, wherein the concentration of the compound of formula (IV) is between about 0.003 and about 0.03 wt%.

19. A compound of formula:



(IV)

wherein:

R_1 = H; C_1-C_{12} straight-chain or branched alkyl; C_1-C_{12} straight-chain or branched acyl; C_3-C_8 cycloalkyl; or a cationic salt moiety;

R_2, R_3 = H, or C_1-C_5 straight-chain or branched alkyl; or R_2 and R_3 taken together may represent O;

X = O;

---- represents any combination of a single bond, or a *cis* or *trans* double bond for the alpha (upper) chain; and a single bond or *trans* double bond for the omega (lower) chain;

R_9 = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

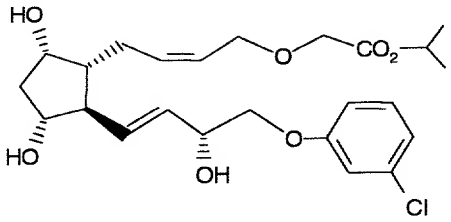
R_{11} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

Y = O; or H and OR_{15} in either configuration wherein R_{15} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl; and

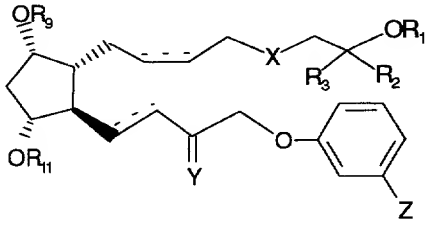
Z = Cl or CF_3;

with the proviso that when R_2 and R_3 taken together represent O, then $R_1 \neq C_1$-C_{12} straight-chain or branched acyl; and when $R_2 = R_3$ = H, then $R_1 \neq$ a cationic salt moiety.

20. The compound of claim 19, having the formula:



21. A compound of formula:



(IV)

wherein:

R_1 = C_1-C_{12} straight-chain or branched alkyl; C_1-C_{12} straight-chain or branched acyl; C_3-C_8 cycloalkyl;

R_2 = R_3 = H;

X = CH_2;

---- represents any combination of a single bond, or a *cis* or *trans* double bond for the alpha (upper) chain; and a single bond or *trans* double bond for the omega (lower) chain;

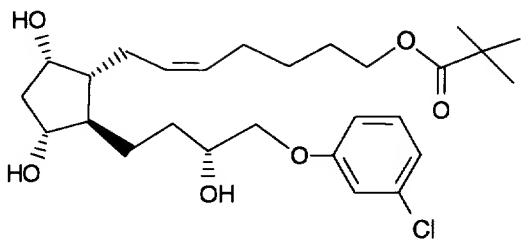
R_9 = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

R_{11} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl;

Y = O; or H and OR_{15} in either configuration wherein R_{15} = H, C_1-C_{10} straight-chain or branched alkyl, or C_1-C_{10} straight-chain or branched acyl; and

Z = Cl or CF_3.

23. The compound of claim 21, having the formula:



ABSTRACT OF THE DISCLOSURE

Disclosed is the use of cloprostenol and fluprostenol analogues for the treatment of glaucoma and ocular hypertension. Also disclosed are ophthalmic compositions comprising said compounds.

IN THE UNITED STATES PATENT OFFICE

In re: Klimko et al.

Serial No: 08/769,293

Filed: December 18, 1996

Examiner: NYA

Group Art Unit: 1209

For: USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

CERTIFICATE OF MAILING BY EXPRESS MAIL

I hereby certify that this correspondence is being deposited with the United States Posta' Service as Express Mail No. EM455926259US in an envelope addressed to: Assistant Commissioner for Patents, Box Issue Fee, Washington, D.C. 20231 on this date:

Date: 4-24-97

Name: Dawn Fedyniak
Dawn Fedyniak

PETITION FOR CORRECTION OF INVENTORSHIP UNDER 37 CFR §1.48(a)

Assistant Commissioner for Patents
BOX ISSUE FEE
Washington, DC 20231

Sir:

Applicants hereby petition to amend the above referenced application to name all of the actual inventors, one of whom was inadvertently omitted upon the filing of the parent application to the present application. In accordance with 35 CFR § 1.48(a), this Petition is accompanied by:

1. A Statement Of Facts verified by the original named inventors establishing when the error, without deceptive intention, was discovered and how it occurred;

2. A Declaration by each of the actual inventors, as required by 37 CFR § 1.63; and

3. The written consent of Alcon Laboratories, Inc., the assignee of record.

The Commissioner is authorized to deduct the $130 processing fee for the Petition pursuant to 37 CFR § 1.17(h). The Commissioner is also hereby authorized to charge any additional fees which may be required or to credit any overpayment to Deposit Account No. 01-0682. A duplicate copy of this letter is attached.

Respectfully submitted,

ALCON LABORATORIES, INC.

Date: 4-24-97

By: Barry L. Copeland
Reg. No. 34,801

Patent Department (Q-148)
Alcon Laboratories, Inc.
6201 South Freeway
Fort Worth, Texas 76134
(817) 551-4322

Atty. Docket No. 1407A

IN THE UNITED STATES PATENT OFFICE

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Date: 4-24-97

Name: Dawn Fedyniak
Dawn Fedyniak

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For: USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

STATEMENT OF FACTS IN SUPPORT OF PETITION FOR CORRECTION OF INVENTORSHIP UNDER 37 CFR §1.48(a)

Assistant Commissioner for Patents
BOX ISSUE FEE
Washington, DC 20231

Sir:

We, **Peter G. Klimko, John E. Bishop, and Verney L. Sallee**, hereby declare and say as follows:

1. We are the originally named inventors of the above-identified application, which is assigned to Alcon Laboratories, Inc.

2. The above-identified application discloses and claims methods and compositions for treating glaucoma and ocular hypertension utilizing analogs of cloprostenol and fluprostenol. The present application is a continuation of U.S. Application Serial No. 08/280,681 filed July 26, 1994 (the "Parent Application"). We

understand that shortly after filing the Parent Application, the Alcon Laboratories patent attorney responsible for the matter left the employ of Alcon, and another Alcon patent attorney, Barry Copeland, assumed responsibility for the prosecution of the application.

3. We further understand that when it become apparent that certain claims of the Parent Application might be considered allowable, Dr. Mark Hellberg advised Mr. Copeland of his belief that Dr. Paul W. Zinke, an Alcon scientist, should be considered as a possible joint inventor. Dr. Hellberg is Alcon's prostaglandin research team leader and is familiar with the contributions made by the research scientists to Alcon's prostaglandin related inventions.

4. Subsequent to receiving Dr. Hellberg's suggestion, we understand that Mr. Copeland reviewed the Parent Application file, but was unable to locate any notes of the former patent attorney or any other written information that would provide a basis for the original inventorship determination. We understand that Mr. Copeland then interviewed several of the scientists involved in the research work that led to the present invention, including at least one of the originally named inventors. Based upon his investigation, we understand that Mr. Copeland concluded that Dr. Zinke contributed materially to the present invention and should therefore be named as a joint inventor. We agree.

5. We believe that the former patent attorney, who was making a very diligent effort to finalize a number of patent applications before departing from Alcon, simply neglected to include Dr. Zinke as an inventor in the Parent Application, and that Dr. Zinke should therefore be included as a joint inventor in the present application.

6. Thus, while we in good faith represented ourselves to be the only inventors at the time the Parent Application was originally filed, we did not at that

time fully appreciate the contributions of Dr. Zinke to the invention as claimed, and therefore may have failed to effectively communicate the extent of those contributions to the former patent attorney. It is under these circumstances that Dr. Zinke's name was omitted as a joint inventor on the Parent Application.

7. We affirm our belief that the omission of Dr. Zinke as a joint inventor on the Parent Application was totally inadvertent and without any deceptive intent.

8. Upon information and belief, Mr. Copeland diligently advised the patent examiner handling the Parent Application of his intention to file a Petition for Correction of Inventorship. However, because the Parent Application was then under a final rejection, it was decided that the Petition for Correction of Inventorship should be filed with the present continuation application.

9. For all of the foregoing reasons, we respectfully request that this Petition to include Dr. Paul Zinke as a joint inventor on the present application be granted.

10. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both,

under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

4-14-97
Date

Peter G. Klimko
Peter G. Klimko

09APR97
Date

John E. Bishop
John E. Bishop

April 14 997
Date

Verney L. Sallee
Verney L. Sallee

IN THE UNITED STATES PATENT OFFICE

In re: Klimko et al.

Serial No: 08/769,293

Filed: December 18, 1996

Examiner: NYA

Group Art Unit: 1209

For: USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION

CERTIFICATE OF MAILING BY EXPRESS MAIL

I hereby certify that this correspondence is being deposited with the United States Postal Service as Express Mail No. EM455926259US in an envelope addressed to: Assistant Commissioner for Patents, Box Issue Fee, Washington, D.C. 20231 on this date:

Date: 4-24-97

Name: Dawn Fedyniak

Dawn Fedyniak

CONSENT OF ASSIGNEE IN SUPPORT OF PETITION FOR CORRECTION OF INVENTORSHIP UNDER 37 CFR 1.48(a)

Assistant Commissioner for Patents
BOX ISSUE FEE
Washington, DC 20231

Sir:

Alcon Laboratories, Inc., the assignee of record in the above-identified application, hereby consents to the addition of **Paul W. Zinke** as a co-inventor in the above-identified application. The Assignment in U.S. Patent Application Serial No. 08/280,681, filed July 26, 1994, and parent to the present application, was recorded on September 21, 1994 at Reel 7143, Frame 817-820.

Respectfully submitted,

ALCON LABORATORIES, INC.

Date: April 24, 1997

By: _____
James A. Arno
Vice President
Reg. No. 26,145
Alcon Laboratories, Inc.
6201 South Freeway, Q-148
Fort Worth, TX 76134

Atty. Docket No. 1407A

COPY

COMBINED DECLARATION AND POWER OF ATTORNEY FOR CONTINUATION-IN-PART APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION "

the specification of which:

(X) is attached hereto.

( ) was filed by an authorized person on my behalf on _____.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations ("37 CFR"), Section 1.56 which states: in part:

> *Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is cancelled or withdrawn from consideration, or the application becomes abandoned.*

Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) it establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) it refutes, or is inconsistent with, a position the applicant takes in:

(i) opposing an argument of unpatentability relied on by the office; or

(ii) asserting an argument of patentability

I hereby claim the benefit under Title 35, United States Code ("35 USC"), Section 120, of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Section 112, I acknowledge the duty to disclose material information as defined in 37 CFR, Section 1.56(a), which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status
08/101,598	August 3, 1993	Pending

As to the subject matter of this application which is common to said earlier application, I do not know and do not believe that the same was ever known or used in the United States of America before my invention thereof or patented or described in any printed publication in any country before my invention thereof, or more than one year prior to said earlier application, or in public use or on sale in the United States of America more than one year prior to said earlier application; that said common subject matter has not been patented or made the subject of an inventor certificate issued before the date of said earlier application in any country foreign to the United States of America or on an application filed by me or my legal representatives or assigns more than twelve months prior to said earlier application; and the earliest application(s) for patent or inventor's certificate on said invention filed by me or my legal representatives or assigns in any country foreign to the United States of America is identified below, as well as all other applications (if any) filed more than twelve months prior to the filing date of this application:

NONE.

The priority of the earliest application(s) (if any) filed within a year prior to said pending prior application is hereby claimed under 35 USC Section 119.

As to the subject matter of this application which is not common to said earlier application, I do not know and do not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to the date of this application, or in public use or on sale in the United States of America more than one year prior to the date of this application, and that said subject matter has not been patented or made the subject of an inventor's certificate issued in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to the date of this application, and that the earliest application(s) for patent or inventor's certificate on said subject matter filed by me or my legal representatives or assigns in any country foreign to the United States of America is identified below, as well as all other such applications) (if any) filed more than twelve months prior to the filing date of this application:

NONE.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint James A. Arno, Reg. No. 26,145; Gregg C. Brown, Reg. No. 30,613; Sally Yeager, Reg. No. 32,757; Julie J. L. Cheng, Reg. No. 33,848; Barry L. Copeland, Reg. No. 34,801; Jeffrey S. Schira, Reg. 34,922; and Patrick M. Ryan, Reg. No. 36,263, of ALCON LABORATORIES, INC., 6201 South Freeway, Fort

Worth, Texas 76134, and Robert L. Price, Reg. No. 22,685, of Lowe, Price, LeBlanc & Becker, 99 Canal Center Plaza, Suite 300, Alexandria, Virginia 22314, my attorneys, with full power of substitution and revocation, to prosecute this application and to transact all business in the United States Patent and Trademark Office connected therewith.

Please direct all correspondence concerning this application to: Julie J. Cheng, Patent Department, ALCON LABORATORIES, INC., 6201 South Freeway, Fort Worth, Texas 76134, telephone no. (817) 551-4321.

Full name of joint inventor: Peter G. Klimko

Residence/Post Office Address: 5301 Overton Ridge, #1206
Ft. Worth, Texas 76132

Inventor's Signature: Peter G. Klimko

Date: 7/22/94

Citizenship: United States

Full name of joint inventor: John E. Bishop

Residence/Post Office Address: 18 Chadwick Circle, Apt. B.
Nashua, New Hampshire 03062

Inventor's Signature: John E Bishop

Date: 22 July 1994

Citizenship: United States

Full name of joint inventor: Verney L. Sallee

Residence/Post Office Address: 304 Diamond Lane

Burleson, Texas 76023

Inventor's Signature: Verney L. Sallee

Date: July 29, 1994

Citizenship: United States

Attorney Docket No. 1407

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

"USE OF CLOPROSTENOL AND FLUPROSTENOL ANALOGUES TO TREAT GLAUCOMA AND OCULAR HYPERTENSION "

the specification of which:

( ) is attached hereto.

(X) was filed by an authorized person on my behalf on July 26, 1994, and assigned U.S. Patent Application Serial No. 08/280,681 (the "Parent Application").

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations ("37 CFR"), Section 1.56 which states: in part:

Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is cancelled or withdrawn from consideration, or the application becomes abandoned.

Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) it establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) it refutes, or is inconsistent with, a position the applicant takes in:

(i) opposing an argument of unpatentability relied on by the office; or

(ii) asserting an argument of patentability

I hereby claim the benefit under Title 35, United States Code ("35 USC"), Section 120, of any United States Application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Section 112, I acknowledge the duty to disclose material information as defined in 37 CFR, Section 1.56(a), which occurred between the filing date of the prior application and the national or PCT international filing date of the Parent Application of which the

present application is a file wrapper continuation:

Application Serial No.	Filing Date	Status
08/101,598	August 3, 1993	Issued as U.S. Patent No. 5,510,383

As to the subject matter of this application which is common to said earlier application, I do not know and do not believe that the same was ever known or used in the United States of America before my invention thereof or patented or described in any printed publication in any country before my invention thereof, or more than one year prior to said earlier application, or in public use or on sale in the United States of America more than one year prior to said earlier application; that said common subject matter has not been patented or made the subject of an inventor certificate issued before the date of said earlier application in any country foreign to the United States of America or on an application filed by me or my legal representatives or assigns more than twelve months prior to said earlier application; and the earliest application(s) for patent or inventor's certificate on said invention filed by me or my legal representatives or assigns in any country foreign to the United States of America is identified below, as well as all other applications (if any) filed more than twelve months prior to the filing date of the Parent Application:

NONE.

The priority of the earliest application(s) (if any) filed within a year prior to said pending prior application is hereby claimed under 35 USC Section 119.

As to the subject matter of this application which is not common to said earlier application, as of the date of filing the Parent Application, I did not know and did not believe that the same was ever known or used in the United States of America before my or our invention thereof or patented or described in any printed

publication in any country before my or our invention thereof or more than one year prior to the date of said Parent Application, or in public use or on sale in the United States of America more than one year prior to the date of said application, and that said subject matter has not been patented or made the subject of an inventor's certificate issued in any country foreign to the United States of America on an application filed by me or my legal representatives or assigns more than twelve months prior to the date of said application, and that the earliest application(s) for patent or inventor's certificate on said subject matter filed by me or my legal representatives or assigns in any country foreign to the United States of America is identified below, as well as all other such applications) (if any) filed more than twelve months prior to the filing date of said Parent Application.

NONE.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint James A. Arno, Reg. No. 26,145; Gregg C. Brown, Reg. No. 30,613; Sally Yeager, Reg. No. 32,757; Barry L. Copeland, Reg. No. 34,801; Jeffrey S. Schira, Reg. 34,922; and Patrick M. Ryan, Reg. No. 36,263, Michael C. Mayo, Reg. No. 38,545 of ALCON LABORATORIES, INC., 6201 South Freeway, Fort Worth, Texas 76134, and Robert L. Price, Reg. No. 22,685, of Lowe, Price, LeBlanc & Becker, 99 Canal Center Plaza, Suite 300, Alexandria, Virginia 22314, my attorneys, with full power of substitution and revocation, to prosecute this application

and to transact all business in the United States Patent and Trademark Office connected therewith.

Please direct all correspondence concerning this application to: Barry L. Copeland, Patent Department Q-148, ALCON LABORATORIES, INC., 6201 South Freeway, Fort Worth, Texas 76134, Telephone No. (817) 551-4322.

Full name of joint inventor:	**Peter G. Klimko**
Residence/Post Office Address:	2115 Pembroke Drive Fort Worth, Texas 76110
Inventor's Signature:	Peter G Klimko
Date:	4-13-97
Citizenship:	United States

Full name of joint inventor:	**John E. Bishop**
Residence/Post Office Address:	878 Townsend Road Groton, Massachusetts 01450
Inventor's Signature:	John E Bishop
Date:	08 Apr 97
Citizenship:	United States

Full name of joint inventor: **Verney L. Sallee**

Residence/Post Office Address: 304 Diamond Lane
Burleson, Texas 76028

Inventor's Signature: Verney L Sallee

Date: April 14, 1997

Citizenship: United States

Full name of joint inventor: **Paul W. Zinke**

Residence/Post Office Address: 4129 Willow Way Road
Fort Worth, Texas 76133

Inventor's Signature: Paul W. Zinke

Date: April 21, 1997

Citizenship: United States

Attorney Docket No. 1407A